Poststarvation hyperphagia and body fat overshooting in humans: a role for feedback signals from lean and fat tissues1–3

Abdul G Dulloo, Jean Jacquet, and Lucien Girardier

ABSTRACT An increase in the sensation of hunger and overeating after a period of chronic energy deprivation can be part of an autoregulatory phenomenon attempting to restore body weight. To gain insights into the role of fat and lean tissue depletion as determinants of such a hyperphagic response in humans, we reanalyzed the individual data on food intake and body composition available for the 12 starved and refed men in the classical Minnesota Experiment after a shift from a 12-wk period of restricted refeeding to an ad libitum refeeding period of 8 wk. For each individual, the following were determined: 1) the total hyperphagic response during the ad libitum refeeding period, calculated as the energy intake in excess of that during the prestarvation (control) period; 2) the degree of fat recovery and that of fat-free mass (FFM) recovery before ad libitum refeeding, calculated as the deviation in fat and FFM from their respective prestarvation values (ie, the amount of fat or FFM before ad libitum refeeding as a percentage of fat or FFM during the control period); and 3) the deficit in energy intake before ad libitum refeeding, calculated as the difference between the energy intake during the period of restricted refeeding and that during the control period. The results indicate that 1) the total hyperphagic response is inversely correlated with the degree of fat recovery (r = −0.6) as well as with that of FFM recovery (r = −0.5), 2) the correlation between hyperphagia and FFM recovery persists after adjustment for fat recovery, and 3) the correlations between hyperphagia and fat recovery or FFM recovery persist after adjustment for the variance in the energy deficit during the preceding period of restricted refeeding. Taken together, these results in humans suggest that poststarvation hyperphagia is determined to a large extent by autoregulatory feedback mechanisms from both fat and lean tissues. These findings, which have implications for both the treatment of obesity and for nutritional rehabilitation after malnutrition and cachexia, have been integrated into a compartmental model of autoregulation of body composition, and can be used to explain the phenomenon of poststarvation overshoot in body fat.


KEY WORDS Body composition, obesity, appetite, thermogenesis, malnutrition, energy partitioning, nutritional rehabilitation

INTRODUCTION

Every year millions of obese individuals diet to lose weight (1), but the long-term prognosis of such therapeutic dieting is poor (2) because in most of them the obese state is reestablished rather rapidly, with body weight often exceeding the predieting value. Such rapid fat restoration and weight “overshooting” have also been observed in normal-weight individuals after a period of food deprivation, eg, during the rehabilitation of famine victims and emaciated prisoners of World War II (3, 4) and during rehabilitation after experimental starvation (5, 6). In their classic Minnesota study in normal-weight men subjected to long-term experimental semistarvation and refeeding, Keys et al (7) went to the extent of describing this phenomenon as poststarvation obesity.

The physiologic basis underlying this phenomenon of excessive fat restoration in human subjects remains poorly understood. Although it is believed to reflect the outcome of a regulatory process geared toward accelerating weight recovery through increases in the hunger and appetite drive (ie, hyperphagia) and in metabolic efficiency (ie, through suppression of thermogenesis) (8–13), the underlying factors that signal and dictate the pattern of these compensatory changes in energy intake and energy expenditure during the dynamic phase of weight recovery remain elusive. In particular, there is little quantitative information available regarding the relative importance of fat and lean tissue depletion as determinants of hyperphagia or thermogenesis, such that their role as compensatory mechanisms within an overall autoregulatory process for the restoration of body weight and body composition remain ill-defined.

Progress in this area of human energetics is hampered by the necessity to conduct longitudinal studies in which food intake, energy expenditure, and body composition are documented before weight loss and at various time points during the dynamic phase of weight regain. Because this type of long-term study is difficult to conduct in humans, mainly because of ethical reasons and the practical constraints associated with long-term compliance with experimental procedures, we there-

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Received June 25, 1996. Accepted for publication October 11, 1996.
Before reanalyzing the Minnesota Experiment on long-term semistarvation and subsequent rehabilitation conducted at the end of World War II. This unique longitudinal study in healthy young men is indeed reputed for being meticulous in details and conducted under tightly controlled conditions of diet and lifestyle.

In a previous paper we reported the results of our reanalysis of the individual data from the Minnesota Experiment on dynamic changes in body composition and basal metabolic rate in the 32 volunteers who completed the 24 wk of semistarvation and subsequent restricted refeeding for 12 wk (14). Evidence was presented suggesting that interindividual variability in the pattern of lean and fat tissue deposition during weight recovery is to a large extent determined by two autoregulatory control systems, as outlined below:

1) One control system operates via the control of energy partitioning between lean and fat tissue compartments, which, as proposed earlier by Payne and Dugdale (15, 16), is an individual characteristic because the fraction of total body energy mobilized or stored as protein (referred to as the P-ratio) varies among individuals but is relatively constant within a given adult individual. Although support for this notion of interindividual variability and intraindividual constancy of the P-ratio was derived from data of prolonged fasting (17), the reanalysis of the Minnesota Experiment using both statistical and numerical approaches provided direct evidence that the individual’s characteristic P-ratio during weight loss is conserved during weight recovery, and that the most important predictor of the P-ratio is the percentage body fat before weight loss (14).

2) The other control system operates via a reduction in thermogenesis in which the magnitude is proportional to the degree of fat depletion but not to that of lean tissue depletion (14). This suggested that the functional importance of the economy in thermogenesis during weight recovery was to accelerate specifically the replenishment of the fat stores, thereby contributing to the disproportionate rate of fat relative to lean tissue recovery.

In the present paper, this reanalysis of data from the Minnesota Experiment has been extended to the second part of the refeeding period during which the subjects were found to develop marked hyperphagia when allowed ad libitum access to food. Our main objective was to gain insights into the extent to which the pattern of hyperphagia is determined by changes in the lean and fat tissue compartments. To this end, the individual data on food intake and body composition of the 12 subjects who remained in the laboratory during this period of ad libitum refeeding were reanalyzed with the following specific aims: 1) to determine the real-time relation between the pattern of hyperphagia and the recovery of fat and lean tissue, and 2) to determine the extent to which the depletion of fat and lean tissue compartments at the end of restricted refeeding can predict the degree of hyperphagia during subsequent ad libitum refeeding.

SUBJECTS AND METHODS

General features of the Minnesota Experiment

The details of this experiment, including the procedure for selecting subjects, their lifestyle and diet during the entire study, methods of achieving the desired weight losses, and techniques and limitations for measurements of numerous indexes are well documented in volumes 1 and 2 of The Biology of Human Starvation (7). Listed below is merely a summary of the experimental procedures directly relevant to our reanalysis of data pertaining to the 12 men who, in addition to being among the 32 subjects who completed the 24 wk of semistarvation and the first 12 wk of restricted refeeding, also remained in the laboratory during the first 8-wk period of ad libitum (unrestricted) refeeding.

Subjects

All 12 subjects were young, healthy, white men with no history of any serious disabling disease nor clinical signs of any serious disorders. Their physical characteristics (x ± SD) before semistarvation were as follows: 25 ± 4 y of age (range: 20–33 y), 179 ± 4 cm in height (range: 174–187 cm), 67.5 ± 5.1 kg body wt (range: 62.3–79.3 kg), and 12.6 ± 5.7% body fat (range: 7–25%).

General experimental design

The subjects were in continuous residence (in the laboratory and living quarters) at the University of Minnesota during the 12-wk control period (C1-C12), 24 wk of semistarvation (S1-S24), 12 wk of restricted rehabilitation (R1-R12), and 8 wk of unrestricted refeeding (R13-R20). In addition to strict adherence to the activity schedule and no access to food except that provided by the investigators throughout these various phases, the subjects were not allowed outside the laboratory or living quarters between S10 and R7 unless supervised. The total loss of body weight—a decrease in gross body weight of 20–26% of original body weight—reproduced the conditions of severe food restriction and is comparable with values found in severe famine. At the beginning of the rehabilitation, these 12 subjects were included in one of four energy groups: group Z (n = 4), group L (n = 2), group G (n = 2), and group T (n = 4), with the energy value of the basic rehabilitation diets supplied to these groups differing by equivalent steps of ∼1420 kJ/d, and increasing from group Z (9950 kJ/d) to group T (14 190 kJ/d). This was in line with one of the main objectives of the experiment, which was to determine what effect the energy level of refeeding had on the rate of rehabilitation during this 12-wk period of restricted refeeding (R1-R12). The subjects were then allowed an unrestricted amount of food while continuing to reside at the University of Minnesota for an additional 8 wk (R13-R20).

Diets

The food was prepared and served under the direct and constant supervision of a trained dietitian, and carefully weighed portions of the food items were served to each subject. At frequent intervals, a complete day’s serving of all food items, including fluids, was collected, weighed, ground, and thoroughly mixed, and samples were taken for chemical analysis. The basic diet for the control period provided an average daily intake of 15.1 MJ: ∼13% of energy as protein, 37% as fat, and 50% as carbohydrate. The semistarvation diet was designed to represent as nearly as possible the type of foods used in European famine areas, and provided an average daily energy intake of 6.61 MJ: 25% of energy as protein, 17% as fat,
and 58% as carbohydrate. The basic rehabilitation diets during the period of restricted refeeding (R1-R12) were in general the same ones used in the semistarvation period, except that more of each food item was given. Groups Z, L, G, and T were refed different amounts of energy, but even in the highest energy group (group T), energy intakes were still deficient relative to that consumed in the control period. Strict dietary control ended at R12 and was followed by ad libitum access to food, with the amount and type of all food eaten carefully recorded during the subsequent 8 wk. The average energy intake was 20 MJ/d: 14% of energy as protein, 35% as fat, and 51% as carbohydrates.

Tests and measurements

Body weight was measured on a beam balance, and body fat was determined by hydrodensitometry. Corrections of body fat and fat-free mass (FFM) for increased hydration and the relative mass of bone at the end of semistarvation and during refeeding were also possible on the basis of formulas provided by Keys et al (7); and derived from a small group of the Minnesota men in whom extracellular fluid space was determined at the end of semistarvation and at frequent intervals during refeeding by the thiocyanate dilution technique.

Present data analysis

Source of individual data

For each of the 12 men who consented to remain in the laboratory after being shifted from restricted refeeding to ad libitum refeeding, individual data on energy intake, body weight, and body fat at various time points during the course of the study were obtained from Tables 449, 450, and 457, respectively, in the Appendix of volume 2 of The Biology of Human Starvation (7). All calculations described below were made on individual data.

Deviations in energy intake

For each subject, the control energy intake (CEI)—ie, the energy intake during the control period—is taken as that consumed by the subject during the last 3 wk of the control period (ie, C10-C12), during which the subjects maintained a relatively constant body weight. CEI = (∑ CEI_wk)/3

where wk is weeks 10–12.

Hyperphagia during ad libitum (AL) refeeding on a week-to-week basis [delta AL (DAL) R wk] is calculated by subtracting the CEI from the weekly energy intake (AL R wk) corresponding to R13, R14, R15, etc, up to R20:

R13 - CEI

DAL R wk = AL R wk - CEI

where wk is weeks 13–20.

The total hyperphagic response between R13 and R20, and referred to as integrated hyperphagia, is calculated as the energy intake during the entire 8-wk ad libitum refeeding period in excess of the CEI:

Integrated hyperphagia = ∑ DAL R wk

where wk is weeks 13–20, and only if DAL R wk > 0.

The deficit in energy intake during the 12 wk before the ad libitum refeeding period—ie, during restricted refeeding and referred to as “prior energy intake deficit”—is calculated as the difference between the energy intake during this entire period of restricted refeeding (RES R wk) during R1-R12 and the CEI:

Prior energy intake deficit = ∑ (RES R wk - CEI)

where wk is weeks 1–12.

Deviations in body weight and in body composition

For each individual, the data provided for body fat and body weight at the end of the control period (C12), during semistarvation at S12 and S24, and during refeeding at R12 and R20, were used to calculate the FFM of individuals at these time points. Deviations in these three anthropometric indexes—body weight, fat, and FFM—at S12, S24, R12, and R20 are expressed as a percentage of the corresponding control (C12) value. During refeeding at R12 and R20, these deviations in fat and FFM relative to control values are referred to as degrees of fat recovery and FFM recovery, respectively. These data can be calculated by using the following equations:

Fat (% of control) = (fat wk/fat C12) × 100

FFM (% of control) = (FFM wk/FFM C12) × 100

where wk is C12, S12, S24, R12, or R20.

Statistical analysis

Statistical analyses were performed by using the computer software program STATISTIX (version 4.0; Analytical Software, St Paul). The various linear model procedures used included Pearson product-moment correlations for determining linear associations between variables, partial correlation procedures for computing the residual correlation between variables after adjustment for the effects of another set of variables, as well as linear- and stepwise-regression analyses. Curve fittings were performed by using the computer software program PEAKFIT (version 2.0; Jandel Scientific, Rafael, CA). Note that the results of the statistical analyses of data on fat mass and FFM are provided for both with and without correction for changes in excess hydration and relative mass of bones.

RESULTS

Real-time pattern of hyperphagia compared with the recovery of body composition

The overall pattern of changes in mean energy intake, body fat, and FFM (expressed as a percentage of the respective control value) is presented in Figure 1. Body fat decreased markedly during semistarvation, and at S24 it was ~30% of the control value. On refeeding it increased rapidly to reach ~80% of the control value at the end of restricted refeeding (R12), and after 8 wk of ad libitum refeeding at R20 it was found to exceed the control value by 74%. The decrease in FFM during semistarvation was less marked than that observed in fat mass, reaching 83% of the control value at S24 (or 73% if corrected for excess hydration), and increasing progressively such that at the end of restricted refeeding at R12 it was 88% (or 80% if corrected for excess hydration) and after 8 wk of ad libitum refeeding at R20 it was 98% of the control value. After the end
of the restricted refeeding period (at the end of R12), energy intake increased markedly, with the mean value for hyperphagia being \( \sim 50\% \) (range: 45\%-60\%) above the CEI during the first 4 wk of ad libitum refeeding, and then declined during the subsequent 4 wk. It was also observed that when body fat was completely recovered (ie, 100% of the control value), and at which point FFM recovery was still well below the control value, a marked hyperphagia was still evident and seemed to disappear as FFM recovery approached 100% of the control value (Figure 1).

**Predictors of hyperphagia during ad libitum refeeding**

Given the above observation suggesting a possible association between the pattern of hyperphagia and the recovery of the two main body-energy compartments (fat mass and FFM), we examined the extent to which variability among the 12 individuals in the degree of fat recovery (42\%-148\% of the control value) and in FFM recovery (84.3\%-90.4\%) at the end of restricted refeeding could predict the variability in their total hyperphagic response (91\%-448 MJ) during the subsequent 8-wk period of ad libitum refeeding (Figure 2). Simple-regression analysis indicated that the integrated hyperphagia during the 8-wk ad libitum refeeding period (R13-R20) was inversely correlated with the degree of fat recovery \( (r = -0.6) \) as well as that of FFM recovery \( (r = -0.5) \). In other words, the lower the degree of fat or FFM recovery at R12, the greater the subsequent degree of hyperphagia over R13-R20. The correlation between hyperphagia and FFM recovery persisted after adjustment (by partial correlation) for variability in the degree of fat recovery or for the degree of prior energy intake deficit (Table 1). Similarly, the correlation obtained between hyperphagia and fat recovery persisted after adjustment for FFM recovery or for the degree of prior energy intake deficit; in the latter case the correlation coefficient improved to an \( r^2 \) of 0.8. By stepwise-regression analysis (Table 2), integrated hyperphagia was most strongly predicted by the degree of fat recovery, and the three variables together—fat recovery, FFM recovery, and prior energy intake deficit—resulted in an \( r^2 \) of \( \sim 0.8 \). Tables 1 and 2 also indicate that all these correlations obtained by simple-, partial-, and stepwise-regression analyses were practically the same whether the calculations were based on data on fat and FFM recovery uncorrected or corrected for changes in hydration and the relative mass of bones.

**DISCUSSION**

Current notions about the physiologic control systems operating to restore losses in body weight (18) center on the lipostatic theory put forward originally by Kennedy (19) in the 1950s, in which reductions in the body fat stores provide the stimulus (signal) for compensatory increases in food intake and hence accelerate weight recovery. Although an intense drive to overeat for days to weeks has often been observed during weight recovery after war famines, experimental starvation, or therapeutic diet regimens (4\–9), there is very little quantitative data on the relation between voluntary energy intake and body fat restoration in human. To our knowledge, the Minnesota Experiment is the only study that has documented in humans such changes in food intake and in body composition. The present reanalysis of these data provides evidence, for the first time, that the magnitude of poststarvation hyperphagia is a
function of the degree of body fat depletion, such that the
greater the degree of fat depletion (ie, the lower the degree of
fat recovery) the greater the hyperphagic response. Although
these findings are in line with the lipostatic theory of Kennedy
(19), this reanalysis furthermore reveals that poststarvation
hyperphagia is also an inverse function of the degree of lean
tissue depletion, such that, as for body fat, the greater the
degree of lean tissue depletion (ie, the lower the degree of FFM
recovery) the greater the hyperphagic response.

It may be argued that because the changes in body fat are
generally accompanied by changes in FFM in the same direction
(20), the fact that hyperphagia is correlated with both fat
and FFM recovery may simply be a reflection of a strong
autocorrelation between these two variables. However, our
findings that the correlation between hyperphagia and the re-
covery of one of the two compartments was unaltered after
adjustment (by partial correlation) for variability in the other
compartment, suggest that the degree of fat depletion and that
of FFM depletion are two independent determinants of
hyperphagia.

Another potentially confounding variable concerning the
importance of tissue depletion as determinants of hyperphagia
may reside in the fact that the 12 men in the Minnesota
Experiment received different amounts of food supplementation
before ad libitum refeeding, such that variations in their
hyperphagic responses may simply reflect the variations in
their energy intake deficit before ad libitum refeeding. In fact,
Keys et al (7) pointed out that the effect of dietary energy
intake in the first 12 wk of restricted rehabilitation was evident
from the food intake during the subsequent ad libitum refeed-
ing period from R13 to R20. During these 8 wk the six men
who from R1 to R12 were placed in the two lower-energy
groups (G and T). However, our reanalysis indicated that after
adjustment for the varying degrees of the prior energy intake
deficit, the correlations between hyperphagia and fat recovery
or FFM recovery still persisted. They actually improved,
thereby suggesting that the drive to overeat after food restric-
tion is not only determined by psychophysiologic responses to
the prior degree of food deprivation per se, but also by the
to the extent to which both fat and FFM are depleted. In fact, the
results of stepwise-regression analysis indicated that of the
tree determinants for poststarvation hyperphagia, it is the
degree of fat recovery that was the strongest, with a significant
contribution from the FFM recovery as well. Consequently, the
possibility arises that feedback loops between the state of
depletion of the fat and FFM compartments and the hunger and
appetite centers in the central nervous system play a central
role in poststarvation hyperphagia. In other words, a consider-
able component of the hyperphagic response to chronic energy
deprivation can be regarded as the outcome of an autoregulat-
tory control system that contributes to restore body weight and
body composition.

Evidence for the existence of two other autoregulatory con-
trol systems, one operating through the control of energy
partitioning and the other through the control of thermogenesis,
was presented previously after the first part of our reanalysis of
the Minnesota Experiment (14). These three control systems
operating through energy partitioning, thermogenesis, and hun-
erg and appetite were incorporated into a conceptual model of
autoregulation of body weight and body composition (Figure
3) and are outlined below.

1) Energy partitioning between lean and fat tissue compart-
ments was shown to be a characteristic of the individual on
the basis that for a particular individual the fraction of the
total body energy mobilized as protein during weight loss
(referred to as the semistarvation P-ratio) was strongly
correlated with the fraction of body energy deposited as
protein during weight recovery (referred to as the refeeding
P-ratio). In other words, individuals with a low P-ratio
during weight loss also had a low P-ratio during weight
recovery, and the converse held true in that those with a
high P-ratio during weight loss also had a high P-ratio
during weight recovery. Furthermore, the data on the pre-
dictors of P-ratio revealed that the initial body composition
(more specifically percentage body fat) before weight loss
was the most important determinant of interindividual vari-
ability in the P-ratio ($r = -0.94$), such that the higher the
initial percentage body fat the lower the fraction of energy

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**TABLE 1**

Regression analysis of the total hyperphagic response (integrated hyperphagia) versus fat recovery, fat-free mass (FFM) recovery, and the prior energy intake deficit

<table>
<thead>
<tr>
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<th>Integrated hyperphagia versus</th>
<th>Integrated hyperphagia versus/</th>
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<tbody>
<tr>
<td></td>
<td>Fat recovery</td>
<td>FFM recovery</td>
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<tr>
<td></td>
<td>$r$</td>
<td>$r$</td>
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<tr>
<td>Uncontrolled</td>
<td>-0.57</td>
<td>-0.53</td>
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<tr>
<td>Partial correlations</td>
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<tr>
<td>adjusted for</td>
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<tr>
<td>FFM recovery</td>
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<td>-</td>
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<tr>
<td>Fat recovery</td>
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<td>-0.44</td>
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<tr>
<td>Prior energy intake deficit</td>
<td>-0.81</td>
<td>-0.60</td>
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</tbody>
</table>

/ Results are based on data on fat and FFM corrected for changes in hydration and relative bone mass.

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**TABLE 2**

Stepwise-regression analysis of the total hyperphagic response (integrated hyperphagia) versus fat recovery, fat-free mass (FFM) recovery, and the prior energy intake deficit

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>$r^2$</th>
<th>$r^2$&lt;sup&gt;1&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Fat recovery (step 1)</td>
<td>0.32</td>
<td>0.32</td>
</tr>
<tr>
<td>Prior energy intake deficit (step 2)</td>
<td>0.68</td>
<td>0.68</td>
</tr>
<tr>
<td>FFM recovery (step 3)</td>
<td>0.79</td>
<td>0.79</td>
</tr>
</tbody>
</table>

<sup>1</sup> Results are based on data on fat and FFM corrected for changes in hydration and relative bone mass.
mobilized as protein, and hence the greater the propensity to mobilize fat during weight loss and to subsequently deposit fat during weight recovery. Taken together, these findings 1) provide direct evidence in support of the proposal originally put forward by Payne and Dugdale (15, 16) that the P-ratio varies between individuals but is relatively constant within a given adult individual, at least during a cycle of weight loss and weight recovery; and 2) led us to the concept that the percentage body fat before weight loss provides a “fat-lean compartmental memory” that defines the P-ratio of the individual and dictates not only the pattern of lean and fat tissue mobilization during energy deficit, but also the way that energy deposited during refeeding is repartitioned into lean and fat tissue compartments.

2) Thermogenesis (assessed as the change in basal metabolic rate adjusted for changes in FFM or for changes in both FFM and fat mass), well known to be diminished during weight loss (7, 8, 10), was also suppressed during weight recovery, and by a magnitude that was proportional to the degree of fat depletion, but was unrelated to the degree of FFM depletion (14). This led to the concept of the existence of a memory of the largest fat stores reached in a given individual, ie, a “fat-stores memory” that governs the suppression of thermogenesis as a function of the replenishment of the fat stores. The functional importance of the economy in thermogenesis during weight recovery is therefore to accelerate specifically the replenishment of the fat stores, thereby contributing to the disproportionate rate of fat relative to lean tissue recovery. Such a mechanism that accelerates the replenishment of fat stores rather than diverting the energy thus saved toward accelerating body protein recovery would have survival value in subsistence societies. This is because (by virtue of the fact that body fat has a greater energy density and a lower energy cost of synthesis and maintenance than does protein) it would provide the organism with a greater capacity to rapidly rebuild an efficient energy reserve and hence to cope with a recurring shortage of food. In more affluent societies, however, it is counterproductive to the use of low-energy diets in the management of obesity because it facilitates obesity relapse.

3) Hunger and appetite drive leads to hyperphagia during weight recovery, and the magnitude of this hyperphagic response is determined (as discussed above) by the extent to which body fat and FFM are depleted, with the degree of fat depletion being the stronger determinant. The hyperphagic response therefore seems to be dictated not only by a memory of the initial fat stores but also by a memory of the initial FFM (hence lean tissue) compartment. The functional importance of this increase in the hunger and appetite sensation, with consequential hyperphagia, is to accelerate the restoration of both lean and fat compartments, as defined by the energy-partitioning characteristic of the individual.

Implications

Our present findings suggesting that the autoregulatory component of the hyperphagic response to energy deprivation goes beyond an explanation based solely on the lipostatic theory, and that it is also governed by the degree of lean tissue depletion, has both theoretical and clinical implications vis-a-vis problems associated with the management of obesity and malnutrition and cachexia. These issues are discussed within the conceptual framework of the proposed compartmental model of autoregulation of body composition depicted in Figure 3.

First, our previous findings that suppression of thermogenesis is inversely related specifically to the recovery of body fat
and not to FFM recovery (14) contrast sharply with our present findings that the control system operating through increased hunger and appetite is related to both fat and FFM recovery. This differential relation of hyperphagia and suppressed thermogenesis vis-à-vis the two tissue compartments during weight recovery suggests that there is an asymmetry in the way that lean and fat tissues are recovered, with fat being recovered at a faster rate than lean tissue. This explains why fat recovery in the Minnesota men reached 100%, FFM recovery was incomplete (Figure 1). Because, as suggested here, the depletion of FFM can also drive hyperphagia, a consequence of the delay in achieving 100% FFM recovery (relative to 100% fat recovery) is that the hyperphagia is prolonged until FFM is fully recovered. Because the proportion of extra energy stored as protein (energy partitioning) is relatively a constant for an individual, 100% FFM recovery can only be achieved if more body fat is deposited, hence accentuating the phenomenon of fat overshooting. Simplistically, it can be said that fat overshooting is a consequence of a delayed protein repletion resulting from the suppression of thermogenesis favoring specifically the replenishment of the fat stores.

Second, a role for lean tissue depletion in the poststarvation hyperphagic response also has direct implications for the treatment of obesity because it raises the possibility that approaches (dietary, behavioral, or pharmacologic) that limit the loss of lean tissue are likely to reduce the hunger drive and hence improve the efficacy of dietary slimming regimens. On the other hand, the findings here that lean tissue depletion is a weaker determinant of the hyperphagic response than is fat depletion may also have clinical implications vis-à-vis the difficulties of recovering lean tissue (and hence bodily functions) during nutritional rehabilitation of malnourished and cachexic patients. These pathophysiologic states are often characterized by poor appetite, with a tendency for the weight gain to be disproportionately high in fat relative to lean tissue (21–28). Consequently, on the basis that the degree of fat depletion is the strongest determinant of the hyperphagic response, approaches that maintain fat stores in a state of depletion are likely to provide a stronger drive to eat, and thereby promote lean tissue recovery in these patients.

In conclusion, the results of the reanalysis of the Minnesota data suggest that human poststarvation hyperphagia has an important autoregulatory component with a feedback loop not only from the fat mass but also from the protein mass. A better understanding of the physiologic and molecular basis of these feedback loops, particularly the identification of the signals linking these two main body-energy compartments to the control of food intake, will be invaluable in the design of novel and more effective strategies for improving lean and fat tissue recovery in malnourished and cachexic patients, as well as for countering the relapse of obesity and its associated health hazards.

REFERENCES